

Exhibit A

(09/671,104)

# Novel 3 $\alpha$ -(Diphenylmethoxy)tropane Analog: Potent Dopamine Uptake Inhibitors without Cocaine-like Behavioral Profiles<sup>†</sup>

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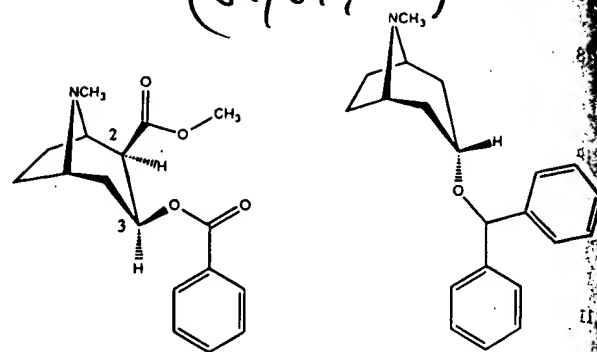
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Novel dopamine uptake inhibitors have proven to be useful tools for investigating the role of the dopamine transporter in the pharmacology of cocaine.<sup>1-10</sup> Cocaine (1) and structurally related analogs bind to the dopamine transporter, and the behavioral effects related to cocaine abuse appear to be mediated through these sites.<sup>11-14</sup>

Systematic structure-activity relationships for a large series of cocaine analogs have primarily been provided by Carroll and colleagues.<sup>3</sup> Recently, attention has been focused on the importance and functionality of the 2-position on the tropane ring.<sup>6,7,15,16</sup> The original work by Lewin et al.<sup>17</sup> suggested that a 2 $\beta$ -ester or equivalent was necessary for high-affinity binding to the cocaine recognition site. Small alkyl ketones in the 2 $\beta$ -position resulted in highly potent and enzymatically stable cocaine analogs.<sup>7</sup> Replacement of the 2 $\beta$ -methyl ester with a vinyl group resulted in potent cocaine analogs and argued against the proposal that hydrogen bonding at this place is important,<sup>6</sup> as previously postulated.<sup>3,17</sup> Recently, analysis of the cocaine receptor site by three-dimensional Voronoi site modeling postulated that the 2-substituent may not impart significant activity to these compounds.<sup>18</sup>

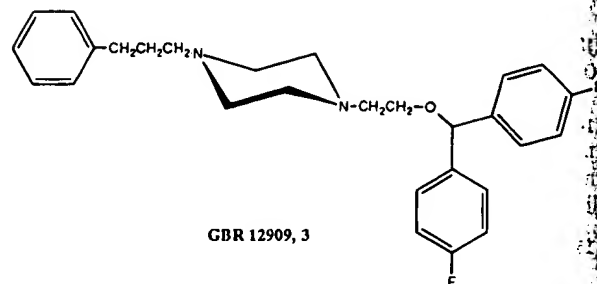
Benztrapine (2, 3 $\alpha$ -(diphenylmethoxy)-1 $\alpha$ H,5 $\alpha$ H-tropane) is a dopamine uptake inhibitor,<sup>19-21</sup> equipotent to cocaine, that exhibits CNS stimulant activity in animal models.<sup>22-24</sup> The combination of a tropane ring, as found in cocaine, with the diphenyl ether function, as found in the potent series of aryl 1,4-dialkyl(en)ylpiperazine dopamine uptake inhibitors, i.e., GBR 12909 (3),<sup>20</sup> suggested that the molecule 2 may be an interesting template for the design of novel dopamine uptake inhibitors. We were also intrigued by the fact that this tropane analog, unlike cocaine and related analogs, lacks a substituent in the 2-position and yet blocks dopamine uptake.<sup>25</sup>

4'-Chloro-3 $\alpha$ -(diphenylmethoxy)tropane (7a) has been reported to be a more potent dopamine uptake inhibitor than its unsubstituted parent drug, 2 (IC<sub>50</sub> = 15 nM versus 140 nM).<sup>20</sup> In addition it is more potent at inhibiting dopamine uptake than serotonin or norepinephrine,<sup>20</sup> suggesting that the 4'-substituent on at least one of the phenyl rings may be important for this improved potency and selectivity. To further explore whether this position is an appropriate target for preparing novel dopamine uptake inhibitors, a series of 4'-substituted analogs of 3 $\alpha$ -(diphenylmethoxy)tropane was synthesized and evaluated for (1) displacement of [<sup>3</sup>H]WIN 35,428 (2 $\beta$ -carbomethoxy-3 $\beta$ -(4-fluoro-



COCAINE, 1

BENZTRAPINE, 2

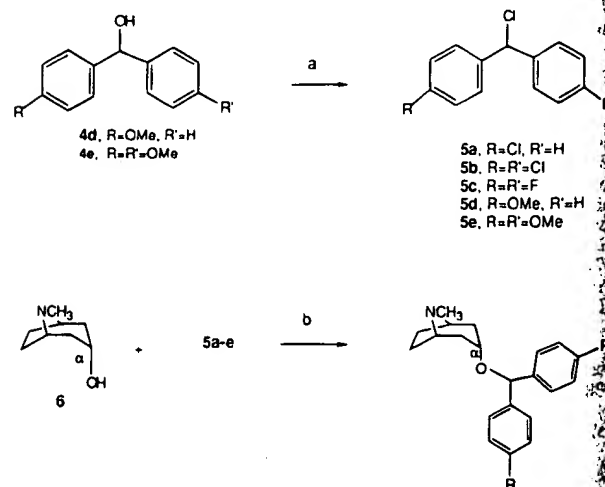


GBR 12909, 3

rophenyl)tropane) binding in rat caudate-putamen, (2) inhibition of [<sup>3</sup>H]dopamine uptake in rat caudate-putamen, (3) stimulation of ambulatory activity in mice which is a characteristic effect of psychomotor stimulant drugs,<sup>26</sup> and (4) substitution for cocaine in rats trained to discriminate 10 mg/kg of cocaine from saline.<sup>27</sup>

The 3 $\alpha$ -(diphenylmethoxy)tropane analogs (7a-e) were prepared generally through either the commercially available (5a-c) or prepared (5d,e) para-substituted benzhydryl chlorides and tropane at 160 °C, as depicted in Scheme 1. In Scheme 2, the 3 $\beta$ -(diphenylmethoxy)tropane (10) was prepared in the same way starting with pseudotropine (9), prepared by the

Scheme 1<sup>a</sup>



<sup>a</sup>(a)SOCl<sub>2</sub>; (b) 160 °C

7a, R=Cl, R'=H  
7b, R=R'=Cl  
7c, R=R'=F  
7d, R=OMe, R'=H  
7e, R=R'=OMe

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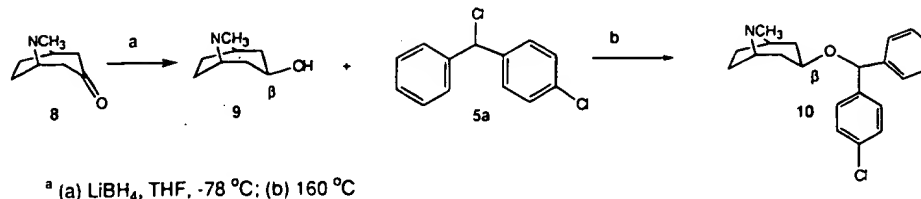
Scheme 2<sup>a</sup>

Table 1. Physical Properties of Compounds 7a-e and 10

compd no.	rec solv	mp, °C	MS	formula	% yield
7a	2-PrOH	212–214	M + 341	C <sub>21</sub> H <sub>25</sub> NOCl <sub>2</sub>	74
7b	acetone	217–219	M + 375	C <sub>21</sub> H <sub>24</sub> NOCl <sub>3</sub>	70
7c	acetone	198–199	M + 343	C <sub>21</sub> H <sub>24</sub> NOF <sub>2</sub> Cl·0.75H <sub>2</sub> O	83
7d	EtOAc	115–117	M + 337	C <sub>22</sub> H <sub>28</sub> NO <sub>2</sub> Cl·0.5H <sub>2</sub> O	63
7e	acetone	180–181	M + 367	C <sub>23</sub> H <sub>30</sub> NO <sub>3</sub> Cl	64
10	acetone	124–126	M + 341	C <sub>21</sub> H <sub>25</sub> NOCl <sub>2</sub> ·0.25H <sub>2</sub> O	31

Table 2. Affinities of Compounds for Binding to the Dopamine Transporter and IC<sub>50</sub> Values for Blockade of [<sup>3</sup>H]Dopamine Uptake in Rat Caudate-Putamen<sup>a</sup>

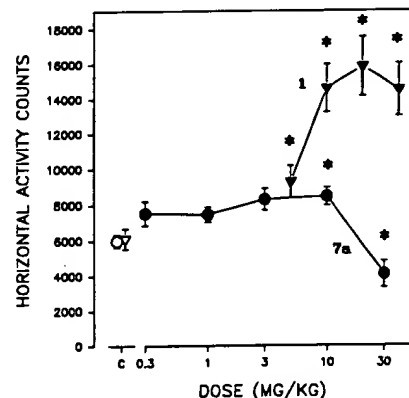
compound	[ <sup>3</sup> H]WIN 35,428 K <sub>i</sub> , nM (% error)	[ <sup>3</sup> H] DA uptake IC <sub>50</sub> , nM
1, <sup>b</sup> cocaine	32(16), 388(57)	12, 3254
3, <sup>c</sup> GBR 12909	11.6 (31)	5
7c	11.8 (11)	71
7b	20.0 (14)	75
7a	30.0 (12)	115
7d	78.4 (8)	468
2	118 (9)	403
10	854 (7)	3519
7e	2000 (7)	2876

<sup>a</sup> Each value represents data from at least three independent experiments, each performed in triplicate. <sup>b</sup> The binding and uptake inhibition curves for cocaine were best fit by two-site models ( $p < 0.01$ ) so both high- and low-affinity values are reported. For all other compounds a single site model provided the best fit to the data, and therefore a single value is reported. <sup>c</sup> Data from ref 32.

stereoselective reduction of tropinone (8) with LiBH<sub>4</sub>. The products were isolated and purified as the HCl salts. Tabulation of their physical properties can be found in Table 1.

The binding and dopamine uptake data for this series of benztropine analogs are presented in Table 2. All of these compounds monophasically displaced [<sup>3</sup>H]WIN 35,428 binding in rat caudate-putamen with K<sub>i</sub> values ranging from 11.8 to 2000 nM. With the exception of the 4',4''-dimethoxy analog 7e and the 3β-analog, 10, all of the analogs were more potent than the parent compound 2, with the most potent analog being the 4',4''-difluoro analog 7c. The rank order of potency for binding was 7c > 7b > 7a > 7d > 2 > 10 > 7e. This rank order of potency was generally the same for inhibition of [<sup>3</sup>H]dopamine uptake. Interestingly, when the diphenylmethoxy substituent was in the 3β-position (10), as is the 3β-benzoyl group of cocaine, potencies for binding and inhibition of [<sup>3</sup>H]dopamine uptake were decreased by approximately 30-fold (as compared to 7a).

Recently, attention has been directed toward designing compounds that show a high affinity for binding to the dopamine transporter and a low potency for inhibition of dopamine uptake.<sup>10,28</sup> The suggestion is that a compound can be designed that blocks cocaine from binding to the transporter but does not concomitantly prevent dopamine from being transported. If the difference between binding affinity and potency for inhibi-

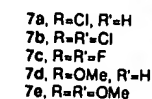
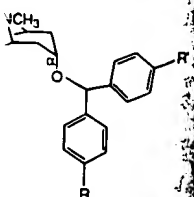
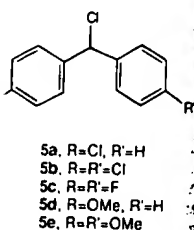


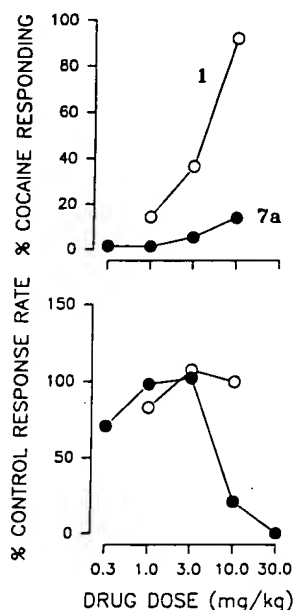
**Figure 1.** Dose-dependent effects of 1 and 7a on locomotor activity in mice. Ordinates: horizontal activity counts after drug administration. Abscissae: dose of drug in mg/kg, log scale. Unfilled points above C represent the effects of saline vehicle controls. Each point represents the average effect determined in eight mice. The data are from the first 30-min period after drug administration, in which the greatest stimulant effects were obtained. The asterisks represent points that are significantly different from vehicle controls.

tion of dopamine uptake is sufficiently large, a functional cocaine antagonist will theoretically result. When the differences between these effects are displayed as ratios of K<sub>i</sub> (or IC<sub>50</sub>) values for binding to IC<sub>50</sub> values for inhibition of dopamine uptake, they must be interpreted with caution. First, the ratio for a given compound can depend on the experimental conditions of the assays.<sup>29,30</sup> Further, these ratios are often presented without statistical indications of variability. Finally, until a compound with a high ratio can be unambiguously distinguished from one with a low ratio, the implication that this ratio is indicative of antagonist activity is not warranted. Therefore, although in this first series of benztropine analogs, the ratios of K<sub>i</sub> to IC<sub>50</sub> values are > 1 and in the case of compound 7c, the ratio is 6, the more compelling observation in our series of compounds comes from the behavioral evaluation of one of the analogs, 7a, which demonstrated a marked difference in its activity from that of cocaine, despite its higher affinity for the cocaine recognition site.

Cocaine, and various dopamine uptake inhibitors, typically increase locomotor activity in rodents. Compound 7a displayed locomotor stimulant activity in mice but was found to be much less efficacious than cocaine (Figure 1). Further, this compound did not substitute for cocaine in rats trained to discriminate 10 mg/kg of cocaine from saline across the range of doses (0.3–10 mg/kg) having behavioral activity (Figure 2). At the highest dose, responding was virtually eliminated, and therefore discriminative effects of 7a could not be assessed.

It is well documented that a variety of cocaine analogs, as well as other structurally diverse dopamine





**Figure 2.** Effects of **1** and **7a** in rats trained to discriminate injections of **1** from saline. Ordinates: percentage of responses on the cocaine-appropriate lever. Abscissae: drug dose in mg/kg (log scale). Top panel: percentage of responses emitted on the lever on which rats were trained to respond after injections of **1**. Bottom panel: rates at which responses were emitted as a percentage of response rate after saline administration. Each point represents the effect in four or six rats.

uptake inhibitors, substitute for the cocaine cue in drug discrimination studies<sup>13,14,31</sup> and in fact these data have supported the important role of this transporter in the pharmacology of cocaine. While the previously studied compounds have provided an immense amount of information regarding the pharmacology and neurochemistry of cocaine, they have differed primarily in potency with all showing a cocaine-like behavioral profile.<sup>13,14,31</sup> Compound **7a** is the first compound to be described that binds with relatively high affinity to the transporter ( $K_i = 30$  nM) but is less efficacious as a locomotor stimulant than cocaine and is not recognized as being cocaine-like in a rat drug discrimination model. Therefore, the unique behavioral profile of compound **7a** in this report may lead to the development of a potential cocaine antagonist.

A comparison of the structure-activity relationships in this series of compounds and the cocaine analogs point to several interesting differences. First, these compounds are not substituted in the 2-position as are all of the potent cocaine analogs reported to date.<sup>3,6,7,15-17</sup> Second, the benzhydryl ether moiety prefers the axial ( $\alpha$ ) stereochemistry which opposes that of cocaine and its active analogs.<sup>3</sup> Third, large differences in potency result from para-substitution on the phenyl ring(s) which is also not observed in the cocaine analogs.<sup>3,9</sup> Finally, these compounds displace [<sup>3</sup>H]WIN 35,428 binding monophasically as opposed to the biphasic displacement seen with cocaine, suggesting that these compounds bind to only one site, whereas cocaine recognizes more than one binding domain on the dopamine transporter. The significant differences in structural requirements for this series of compounds compared to cocaine suggest that there may be different binding domains accessed by these tropane analogs that

may be exploited for future novel probes of the dopamine transporter.

In summary, compound **7a** is the first tropane analog to be described that is structurally similar to cocaine and GBR 12909, binds with high affinity to the dopamine transporter, blocks the reuptake of dopamine, and yet is behaviorally distinct from all other compounds that share this structural and/or neurochemical profile. Preliminary locomotor activity and drug discrimination data show that all of the compounds in this series appear to demonstrate the same behavioral profile as **7a**. The possibility that this compound and others in this series may be potential cocaine antagonists is currently being investigated.

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## References

- (1) Kline, R. H., Jr.; Wright, J.; Fox, K. M.; Eldefrawi, M. E. Synthesis of 3-aryleugonine analogues as inhibitors of cocaine binding and dopamine uptake. *J. Med. Chem.* **1990**, *33*, 2024-2027.
- (2) Milius, R. A.; Saha, J. K.; Madras, B. K.; Neumeyer, J. L. Synthesis and receptor binding of N-substituted tropane derivatives. High-affinity ligands for the cocaine receptor. *J. Med. Chem.* **1991**, *34*, 1728-1731.
- (3) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine receptor: biochemical characterization and structure-activity relationships of cocaine analogues at the dopamine transporter. *J. Med. Chem.* **1992**, *35*, 969-981.
- (4) de Costa, B. R.; George, C.; Dominguez, C. Synthesis of isothiocyanato-1-[1-(2-benzothienyl)cyclohexyl]piperidines, potential irreversible ligands at the dopamine reuptake site. *J. Chem. Soc. Perkin Trans. 1*, **1992**, 1671-1680.
- (5) Deutsch, H. M.; Schweri, M. M.; Culbertson, C. T.; Zalkow, L. H. Synthesis and pharmacology of irreversible affinity labels as potential cocaine antagonists: aryl 1,4-dialkylpiperazines related to GBR-12783. *Eur. J. Pharmacol.* **1992**, *220*, 173-180.
- (6) Kozikowski, A. P.; Roberti, M.; Xiang, L.; Bergmann, J. S.; Callahan, P. M.; Cunningham, K. A.; Johnson, K. M. Structure-activity relationship studies of cocaine: replacement of the C-2 ester group by vinyl argues against H-bonding and provides an esterase-resistant, high affinity cocaine analogue. *J. Med. Chem.* **1992**, *35*, 4764-4766.
- (7) Davies, H. M. L.; Saikali, E.; Sexton, T.; Childers, S. R. Novel 2-substituted cocaine analogs: binding properties at dopamine transport sites in rat striatum. *Eur. J. Pharmacol. Mol. Pharmacol. Sect.* **1993**, *244*, 93-97.
- (8) Rothman, R. B.; Lewis, B.; Dersch, C.; Xu, H.; Radesca, L.; de Costa, B. R.; Rice, K. C.; Kilburn, R. B.; Akunne, H.; Pert, A. Identification of a GBR 12935 homolog LR1111, which is over 4000-fold selective for the dopamine transporter, relative to serotonin and norepinephrine transporters. *Synapse* **1993**, *14*, 34-39.
- (9) Meltzer, P. C.; Liang, A. Y.; Brownell, A.-L.; Elmaleh, D. R.; Madras, B. K. Substituted 3-phenyltropane analogs of cocaine synthesis, inhibition of binding at cocaine recognition sites and positron emission tomography imaging. *J. Med. Chem.* **1993**, *36*, 855-862.
- (10) He, X.-s.; Raymon, L. P.; Mattson, M. V.; Eldefrawi, A. E.; de Costa, B. R. Further studies of the structure-activity relationships of 1-[1-(2-benzothienyl)cyclohexyl]piperidine. Synthesis

- (1) and evaluation of 1-[1-(2-benzo[b]thienyl)N,N-dialkylcyclohexyl- amines at dopamine uptake and phencyclidine binding sites. *J. Med. Chem.* **1993**, *36*, 4075-4081.
- (11) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* **1987**, *237*, 1219-1223.
- (12) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci.* **1991**, *14*, 299-301.
- (13) Balster, R. L.; Carroll, F. I.; Graham, J. H.; Mansbach, R. S.; Rahman, M. A.; Philip, A.; Lewin, A. H.; Showalter, V. M. Potent substituted-3 $\beta$ -phenyltropane analogs of cocaine have cocaine-like discriminative stimulus effects. *Drug Alcohol Depend.* **1991**, *29*, 145-151.
- (14) Cline, E. J.; Terry, P.; Carroll, F. I.; Kuhar, M. J.; Katz, J. L. Stimulus generalization from cocaine analogs with high in vitro affinity for dopamine uptake sites. *Behav. Pharmacol.* **1992**, *3*, 113-116.
- (15) Carroll, F. I.; Abraham, P.; Kuzemko, M. A.; Gray, J. L.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis and cocaine receptor affinities of 3-phenyl-2-(3'-methyl-1,2,4-oxadiazole-5'-yl)tropane isomers. *J. Chem. Soc., Chem. Commun.* **1993**, 44-46.
- (16) Carroll, F. I.; Kotian, P.; Gray, J. L.; Abraham, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. 3 $\beta$ -(4'-Chlorophenyl)- tropan-2 $\beta$ -carboxamides and cocaine amide analogues: new high affinity and selective compounds for the dopamine transporter. *Med. Chem. Res.* **1993**, *3*, 468-472.
- (17) Lewin, A. H.; Gao, Y.; Abraham, P.; Boja, J.; Kuhar, M. J.; Carroll, F. I. 2 $\beta$ -Substituted analogues of cocaine. Synthesis and inhibition of binding to the cocaine receptor. *J. Med. Chem.* **1992**, *35*, 135-140.
- (18) Srivastava, S.; Crippen, G. M. Analysis of cocaine receptor site ligand binding by three-dimensional Voronoi site modeling approach. *J. Med. Chem.* **1993**, *36*, 3572-3579.
- (19) van der Zee, P.; Hespe, W. A. Comparison of the inhibitory effects of aromatic substituted benzhydryl ethers on the uptake of catecholamines and serotonin into synaptosomal preparations of the rat brain. *Neuropharmacology* **1978**, *17*, 483-490.
- (20) van der Zee, P.; Koger, H. S.; Gootjes, J.; Hespe, W. Aryl 1,4-dialk(en)ylpiperazines as selective and very potent inhibitors of dopamine uptake. *Eur. J. Med. Chem.* **1980**, *15*, 363-370.
- (21) Coyle, J. T.; Snyder, S. H. Antiparkinsonian Drugs: Inhibition of dopamine uptake in the corpus striatum as a possible mechanism of action. *Science* **1969**, *166*, 899-901.
- (22) Koe, B. K. Molecular geometry of inhibitors of the uptake of catecholamines and serotonin in synaptosomal preparations of rat brain. *J. Pharmacol. Exp. Ther.* **1976**, *199*, 649-661.
- (23) McKearney, J. W. Effects of dopamine uptake inhibitors on schedule-controlled behavior in the squirrel monkey. *Psychopharmacology* **1982**, *78*, 377-379.
- (24) Acri, J. B.; Seidleck, B.; Witkin, J. M. Effects of dopamine uptake inhibitors on behavioral and toxic effects of cocaine. In *Problems of Drug Dependence 1993*; Harris, L. S., Ed.; NIDA Monograph 141; NIDA: Washington, DC, 1994; p 441.
- (25) Newman, A. H.; Allen, A. C.; Izenwasser, S.; Katz, J. L. Novel 3 $\alpha$ -diphenylmethoxytropane analogs that are unsubstituted in the 2-position are potent dopamine uptake inhibitors. *Soc. Neurosci. Abs.* **1993**, *19*, 752.8.
- (26) Kelleher, R. T. Psychomotor Stimulants. In *Drug Abuse: The Clinical and Basic Aspects*; Pradhan, S. N., Dutta, S. M., Eds.; Mosby: St. Louis, MO, 1977.
- (27) Witkin, J. M.; Nichols, D. E.; Terry, P.; Katz, J. L. Behavioral effects of selective dopaminergic compounds in rats discriminating cocaine injections. *J. Pharmacol. Exp. Ther.* **1991**, *257*, 706-713.
- (28) Simoni, D.; Stoelwinder, J.; Kozikowski, A. P.; Johnson, K. M.; Bergmann, J. S.; Ball, R. G. Methoxylation of cocaine reduces binding affinity and produces compounds of differential binding and dopamine uptake inhibitory activity: discovery of a weak cocaine "antagonist". *J. Med. Chem.* **1993**, *36*, 3975-3977.
- (29) Rothman, R. B.; Becketts, K. M.; Radesca, L. R.; de Costa, B. R.; Rice, K. C.; Carroll, F. I.; Dersch, C. M. Studies of the biogenic amine transporters. II. A brief study on the use of [ $^3$ H]DA-uptake-inhibition to transporter-binding-inhibition ratios for the in vitro evaluation of putative cocaine antagonists. *Life Sci.* **1993**, *53*, PL 267-272.
- (30) Izenwasser, S.; Rosenberger, J. G.; Cox, B. M. The cocaine analog WIN 35,428 binds to two sites in fresh rat caudate-putamen: significance of assay procedures. *Life Sci. Pharmacol. Lett.* **1993**, *52*, PL141-145.
- (31) Kleven, M. S.; Anthony, E. W.; Woolverton, W. L. Pharmacological characterization of the discriminative stimulus effects of cocaine in rhesus monkeys. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 312-317.
- (32) Izenwasser, S.; Terry, P.; Heller, B.; Witkin, J. M.; Katz, J. L. Differential relationships among dopamine transporter affinities and stimulant potencies of various uptake inhibitors. Submitted manuscript.

, Eldefrawi, M. E. Inhibitors of cocaine. *J. Med. Chem.* **1990**, *33*, 2024-2026.

umeyer, J. L. Syn- tropane derivatives. *J. Med. Chem.* **1990**, *33*, 2024-2026.

har, M. J. Cocaine: structure-activity relationships at the dopamine transporter. *J. Med. Chem.* **1990**, *33*, 2024-2026.

ynthesis of isothio- peridines, potential dopamine uptake site. *J. Chem. Soc.* **1990**, *33*, 2024-2026.

, C. T.; Zalkow, L. E. Affinity labels for dopamine uptake sites. *J. Med. Chem.* **1990**, *33*, 2024-2026.

Bergmann, J. S.; Kozikowski, A. P. Structure-activity relationships of the C-2 position of cocaine analogs and provides an insight into the mechanism of action. *J. Med. Chem.* **1990**, *33*, 2024-2026.

lders, S. R. Novel tropane derivatives at dopamine uptake sites. *J. Med. Chem.* **1990**, *33*, 2024-2026.

, Radesca, L.; de Costa, B. R.; Pert, A. Cocaine analogs, which is over 100 times more potent, relative to cocaine. *Synapse* **1993**, *14*, 2024-2026.

; Elmaleh, D. R. Cocaine analogs of cocaine: recognition sites and pharmacological effects. *J. Chem.* **1993**, *36*, 2024-2026.

Eldefrawi, A. E.; de Costa, B. R.; Pert, A. Cocaine analogs, which is over 100 times more potent, relative to cocaine. *Synapse* **1993**, *14*, 2024-2026.

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Eldefrawi, A. E.; de Costa, B. R.; Pert, A. Cocaine analogs, which is over 100 times more potent, relative to cocaine. *Synapse* **1993**, *14*, 2024-2026.